REMARKS

Claims 1 and 3-22 are pending. Claims 16-19 and 22 have been withdrawn from consideration. Claims 8-15, 20 and 21 are allowable. Claims 1 and 3-7 are rejected. Claim 1 has been amended based on the disclosure on page 7, lines 8 and 9. Claim 4 has been amended to conform with the language of claim 1. Claims 1 and 3-22 thus are pending for reexamination and reconsideration, which respectfully are requested in light of the foregoing amendments and following remarks.

Claim 4 is rejected for lack of antecedent basis in claim 1 for "said" toxin. Claim 4 has been amended to recite "said RNase," thereby obviating the rejection.

Claims 1, 6 and 7 are rejected under Section 102(b) over Mallinckrodt Medical, Inc. (WO 94/07535). Specifically, the examiner asserts that the word "therapeutic" in the phrase "therapeutic radionuclide" is "not accorded any patentable weight where it merely recites the purpose of a process of the intended use of a product." As previously argued, however, the word therapeutic in this context defines a particular class of radionuclides and, accordingly, is not merely a recitation of "purpose" or "intended use." Thus, therapeutic radionuclides include high energy beta emitters, alpha emitters, Auger electron emitters and boron conjugates for BNCT. In contrast, Mallinckrodt Medical, Inc. discloses a method of imaging, and states that suitable radioactive labels for use in that method include indium-111, iodine-123 and technetium-99m (page 5, lines 8-11 and examples). All three of these radionuclides emit only gamma radiation, with possible weak beta emission and, accordingly, are useless for therapy. Excerpts from the Handbook of Chemistry and Physics are attached to confirm these statements. Accordingly, applicant maintains that the term "therapeutic" clearly describes the nature of the radionuclide, and distinguishes the radionuclide from those

allegedly disclosed in Mallinckrodt Medical Inc., and requests withdrawal of the rejection. However, solely to advance prosecution, applicant has amended claim 1 to recite that the therapeutic radionuclide is an alpha-emitter or beta-emitter. Mallinckrodt Medical, Inc. does not describe conjugates with alpha- or beta-emitters and, therefore, the rejection may be withdrawn.

Claims 1, 3, 6 and 7 are newly rejected under Section 103(a) over Nicolotti. Specifically, the examiner rejects these claims on the theory that "antigen-antibody complexes are analogous to ligand-cytokine complexes." Presumably, therefore, the examiner asserts that one of ordinary skill in the art would have been motivated to prepare the instantly claimed conjugates in light of the radiolabeled antibody fragments allegedly disclosed by Nicolotti. Applicants respectfully traverse the rejection.

First, Nicolotti neither teaches nor suggests the instantly claimed conjugates of a cytokine with an RNase. Second, the conjugates described by Nicolotti could not have suggested to one of ordinary skill in the art the desirability of preparing the instantly claimed radiolabeled cytokine conjugates. Because there is no evidence that the cited reference would have motivated one of ordinary skill to prepare the claimed conjugates, no *prima facie* case of obviousness is made out, and the rejection should be withdrawn.

Moreover, the instantly claimed radiolabeled conjugates have distinct advantages over those disclosed in Nicolotti. Thus, the radiolabeled conjugate is delivered by pretargeting with a bispecific antibody/cytokine receptor reagent, followed by administration of the conjugate. The conjugate has a low molecular weight and, therefore, is rapidly cleared from the blood. Similar advantages are found in avidin/biotin systems and in the IBC bispecific antibody technology. But, the present invention offers the additional advantage that the conjugate also is rapidly internalized, resulting in increased

retention of the radiometal. It is clear from the instant specification that, for example, the bispecific antibody and IL-15-alpha are pretargeted to the tumor. As noted in the paragraph bridging pages 3 and 4 of the specification: "while internalization is not necessary for a therapeutic radionuclide to be effective, the trimeric complex provides a tighter binding to the malignant cells, and thus improves these modalities as well."

In contrast, Nicolotti uses a directly radiolabeled antibody fragment, which does not have the advantages of pretargeting methodology, and neither teaches nor suggests that retention of internalized radiometal provides superior persistence of the isotope in the tumor. Indeed, Nicolotti utilizes CEA as the exemplified target antigen, which is only very slowly internalized. Moreover, the Nicolotti examples are limited to radiolabeled Fab' conjugates, which have not proven to be useful therapeutic agents because of high uptake/retention of the isotope by the kidney.

In sum, for the reasons set forth above, Nicolotti neither teaches nor suggests the instantly claimed compositions. Accordingly, withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the foregoing amendments and remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

January 7, 2000
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